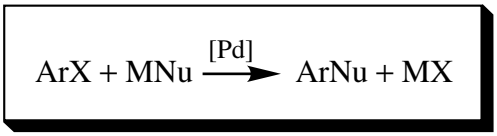

III.2.19 Structural and Mechanistic Aspects of Palladium-Catalyzed Cross-Coupling

CHRISTIAN AMATORE and ANNY JUTAND

A. INTRODUCTION

Palladium catalyzes the C—C bond formation by cross-coupling of aryl halides and nucleophiles.[1]–[8]

$$ArX + MNu \xrightarrow{[Pd]} ArNu + MX$$

Discovered in 1976 with Grignard and organolithium reagents as nucleophiles by Fauvarque and Jutand[9] and Sekiya and Ichikawa,[10] this reaction was successively extended to organozinc,[11] organoaluminum,[1] and organozirconium[1] by Negishi, to organostannanes by Milstein and Stille,[12] and to organoboranes by Miyaura and Suzuki.[13] The first coupling of alkynes reported by Sonogashira and co-workers required Cu^I salts as cocatalysts.[14] Cross-coupling of amides and alkoxides leads to the formation of C—N and C—O bonds as reported simultaneously by Hartwig and co-workers[15]–[18] and Buchwald and co-workers[19]–[21] Stille and Echavarren pioneered the cross-coupling of aryl triflates with nucleophiles.[22]

The mechanism of Pd-catalyzed cross-coupling is generally regarded as proceeding through a succession of four main steps when the palladium is ligated by a monodentate phosphine L (**Scheme 1**).[1],[2],[23] The true catalyst is considered as a 14-electron palladium(0) complex, Pd^0L_2. The first step is an *oxidative addition* of the aryl halide to Pd^0L_2,[24] which gives a σ-arylpalladium(II) complex, *trans*-$ArPdXL_2$,[25],[26] via a fast isomerization of the *cis* complex.[27] The second step is a nucleophilic attack on *trans*-$ArPdXL_2$,[28]–[34] (*transmetallation*), which provides a diorganopalladium(II) complex *trans*-$ArPdNuL_2$,[28],[32],[33] where the palladium(II) is ligated both by the nucleophile and the aryl group. A *trans–cis isomerization* is then required[35]–[37] because the *reductive elimination*, which gives the cross-coupling product together with the palladium(0) catalyst, proceeds from *cis*-$ArPdNuL_2$ complexes.[35]–[37]

When considering monophosphine ligands (**Scheme 1**), the rate-determining step of the catalytic cycle is the oxidative addition[9],[29],[38] for the low reactive aryl bromides or chlorides,[25] whereas for the more reactive aryl iodides, the transmetallation is considered as the rate-determining step.[2],[31],[39] Reductive elimination from *trans*-$ArPdNuL_2$

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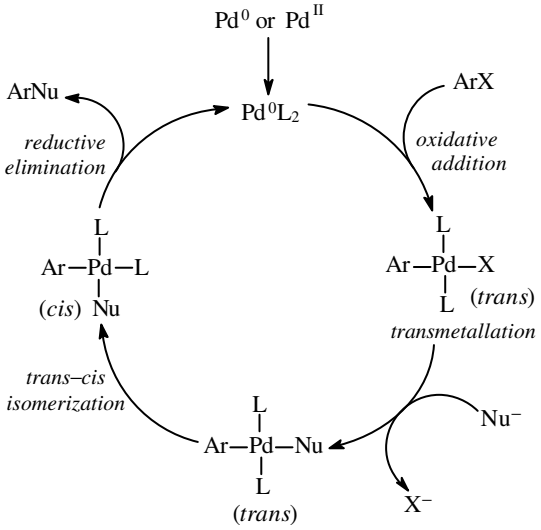


Scheme 1

complexes is also invoked as the rate-determining step due to the required endergonic *trans–cis* isomerization of *trans*-$ArPdNuL_2$.[35]–[37] Reductive elimination from *cis*-diorganopalladium(II) complexes may also be rate determining.[35]

Establishment of the real mechanistic sequences has been an important target owing to its huge synthetic consequences. However, most mechanistic studies (e.g., those on which Scheme 1 is based) have been made on isolated systems, each featuring one step of the postulated cycle, but not in the context of the whole catalytic cycle active in a particular situation. Indeed, the common mechanistic approach consists of investigating elemental steps separately, under stoichiometric conditions, starting from stable isolated complexes: 18-electron palladium(0) complexes, Pd^0L_4, for the oxidative addition[24],[40],[41]; *trans*-$ArPdXL_2$ complexes for the transmetallation[28]–[34]; and *trans*-$ArPdNuL_2$ for the Ar—Nu coupling.[28],[32],[33] Extremely important fundamental results are then available on these individual elemental steps. However, any synthetic chemist knows perfectly well that the subtlety and versatility of the effective catalytic cycle are much more complicated than what the "reconstructed" cycle in **Scheme 1** may predict. Investigation of the reactivity of isolated and consequently stable complexes in elemental steps may give rise to erroneous results because the real elemental catalytic steps may involve highly energetic and thus unstable complexes and may thus proceed quite differently. For example, the synthetically known but mechanistically ignored influence of "innocent" reagents such as *anions* delivered by the aryl halide and/or by the precursor of the palladium(0), *cations* delivered by the nucleophile, and expected *labile ligands* such as olefins borne by the palladium(0) precursor, which are present in catalytic reactions but absent in the isolated investigated steps, are thus deliberately overlooked.

The efficiency of palladium(0) in cross-coupling reactions arises from its ability to activate Ar—X bonds (X = I,[26] Br,[26] Cl,[26] OTf[41]) by an oxidative addition. Different palladium(0) complexes are used as catalysts: either isolated stable palladium(0) complexes such as Pd^0L_4 or complexes generated *in situ* from $Pd^0(dba)_2$ and phosphines.[3]–[8] Palladium(II) complexes, PdX_2L_2 (X = Cl, Br), are also utilized as precursors of palladium(0) complexes.[1]–[8] They are reduced by the nucleophile or by an extra

reducer when the nucleophile is not a reducing reagent.[11] Association of $Pd(OAc)_2$ and phosphines is also a source of palladium(0) in Suzuki reactions.[4] Pd^0L_4 and $PdCl_2L_2$ catalyze the C—C coupling of "hard" and "soft" C-nucleophiles.[1]–[8] Mixtures of $Pd^0(dba)_2$ and phosphines are well adapted to "soft" nucleophiles as in Stille reactions (organostannanes).[3],[5]–[8] Monodentate ligands are efficient for the cross-coupling of nucleophiles, which cannot undergo a β-hydride elimination[9] whereas bidentate ligands are required when the nucleophile is sensitive to β-hydride elimination (see **Scheme 28** in this section).[42] C—O and C—N couplings require either bidentate ligands, which are then introduced with $Pd^0(dba)_2$ or $Pd^0{}_2(dba)_3$, or monodentate bulky ligands such as tri(*ortho*-tolyl)phosphine, P(*o*-Tol)$_3$, which are introduced via Pd^0L_2 or $PdCl_2L_2$ complexes.[17],[18],[21]

Whatever the precursor of the palladium(0), a low ligated 14-electron Pd^0L_2 complex is assumed to be the active species, which initiates the catalytic cycle via an oxidative addition (**Scheme 1**).[24] However, it is often observed that the overall reactivity strongly depends on the precursor of the palladium(0) complex: for example, $PdCl_2(PPh_3)_2$ compared to $Pd^0(dba)_2 + 2PPh_3$.[43] $Pd^0(PPh_3)_4$ appears to be more efficient than $Pd^0(dba)_2 + 2PPh_3$.[44],[45] This suggests that the chloride and the dba attached to the precursor play a role in the catalytic process. Moreover, all reactions are supposed to involve *trans*-$ArPdXL_2$ intermediates in the transmetallation process (**Scheme 1**). However, some nucleophilic attacks on *trans*-$ArPdI(PPh_3)_2$ complexes are slower than the overall catalytic reaction,[9],[29],[30] suggesting that they are not always key intermediates under catalytic conditions. Mechanistic investigations appear crucial to understand the catalytic process, and so improve its efficiency and selectivity.

Mechanisms of Pd-catalyzed cross-coupling are going to be discussed including "stoichiometric" investigations of elemental steps and those made in the context of real catalytic reactions, that is, taking into account all the additives present in a real catalytic reaction: (i) presumed labile ligands such as dba brought by the precursor, (ii) anions arising from the palladium(II) precursors or released in solution from ArX as the catalytic reaction proceeds, and (iii) cations delivered by the nucleophiles or by the reducers of the Pd^{II} complexes.

B. MECHANISM OF THE CROSS-COUPLING CATALYZED BY PALLADIUM(0) COMPLEXES LIGATED BY MONOPHOSPHINE LIGANDS (L)

B.i. Rate and Mechanism of the Oxidative Addition of Aryl Halides to Palladium(0) Complexes as a Function of Their Precursor and the Ligand

B.i.a. ***Pd^0L_4 as a Precursor of Pd^0L_2 ($L = PPh_3$).*** In 1976, $Pd^0(PPh_3)_4$ was the first complex tested as a catalyst in cross-coupling of aryl halides with Grignard and organolithium reagents by Fauvarque and Jutand.[9] The 18-electron complex dissociates in solution into the 16-electron $Pd^0(PPh_3)_3$ and PPh_3 (Eq. 1 of **Scheme 2**).[46] On the basis of kinetic studies, it has been established that the low ligated 14-electron $Pd^0(PPh_3)_2$, formed after a second deligation (Eq. 2 of **Scheme 2**), is the actual reactive species in the oxidative addition step to aryl iodides (Eq. 3 of **Scheme 2**).[24] $Pd^0(PPh_3)_2$ is probably ligated or at least strongly solvated by the solvent, namely, $SPd^0(PPh_3)_2$ (S = THF or DMF). Yet, the usual $Pd^0(PPh_3)_2$ formulation will be used in the following.

Elemental steps

$Pd^0(PPh_3)_4 \rightleftharpoons Pd^0(PPh_3)_3 + PPh_3 \quad K_1/[PPh_3] >> 1 \quad (1)$

$Pd^0(PPh_3)_3 \rightleftharpoons Pd^0(PPh_3)_2 + PPh_3 \quad K_2/[PPh_3] << 1 \quad (2)$

$ArX + Pd^0(PPh_3)_2 \longrightarrow ArPdX(PPh_3)_2 \quad k \quad (3)$

Overall reaction

$ArX + Pd^0(PPh_3)_2 \longrightarrow ArPdX(PPh_3)_2 + 2PPh_3 \quad k_{app} = kK_2/[PPh_3] \quad (4)$

Scheme 2

Despite the high reactivity of $Pd^0(PPh_3)_2$ in the oxidative addition step (Eq. 3 of **Scheme 2**), the overall reaction (Eq. 4 of **Scheme 2**) is slow (**Table 1**, entry 3) because the concentration of $Pd^0(PPh_3)_2$ is maintained at trace levels due to the extremely uphill equilibrium (Eq. 2 of **Scheme 2**), which lies in favor of $Pd^0(PPh_3)_3$, the major but nonreactive species. The rate of the overall oxidative addition (Eq. 4 of **Scheme 2**): $k_{app} = kK_2/[PPh_3]$ decreases when the concentration of PPh_3 increases with a reaction order in PPh_3 of -1.[24] By construction, use of Pd^0L_4 catalysts results in the necessary presence of 2 equiv of phosphine in addition to the active catalytic form Pd^0L_2. Therefore, it was quickly realized that there is an important advantage in bypassing the endergonic equilibrium (Eq. 2 of **Scheme 2**) and in quantitatively generating Pd^0L_2 complexes in the absence of any extra phosphines.

The oxidative addition of *p*-substituted aryl iodides[24],[40] and triflates[41] to $Pd^0(PPh_3)_4$ follows a Hammett correlation with a positive slope and is thus faster for aryl derivatives substituted by electron-withdrawing groups.[26] The following order of reactivity has been established in DMF at 20 °C[41]:

	PhI	>>	PhOTf	>	PhBr	>>	PhCl
k_{app} (M^{-1} s^{-1}) =	16		1.7×10^{-3}		10^{-3}		n.d.

TABLE 1. Comparative Reactivity of Palladium(0) Complexes in Oxidative Addition to Phenyl Iodide as a Function of Precursors (L = PPh_3)[a]

Number	Precursor of Pd^0 (2 mM)	Major Species	Reactive Species	k_{app} (M^{-1} s^{-1})[a] THF (DMF) 20 °C	25 °C
1	$Pd^0(dba)_2 + 4L$	$Pd^0(dba)L_2$	Pd^0L_2	2 (1.3)	
2	$Pd^0(dba)_2 + 2L$	$Pd^0(dba)L_2$	Pd^0L_2	2.7 (1.9)	
3	Pd^0L_4	Pd^0L_3	Pd^0L_2	16 (16)	25 (25)
4	$Pd(OAc)_2 + 3L + 3NEt_3$	$Pd^0L_2(OAc)^-$	$Pd^0L_2(OAc)^-$		(65)
5	$Pd(OAc)_2 + 3L$	$Pd^0L_2(OAc)^-,H^+$	$Pd^0L_2(OAc)^-,H^+$		(140)
6	$PdBr_2L_2 + 2e$	$Pd^0L_2Br^-$	$Pd^0L_2Br^-$	400	
7	$PdCl_2L_2 + 2e$	$Pd^0L_2Cl^-$	$Pd^0L_2Cl^-$	530	
8	$PdCl_2L_2 + 2e + 50Li^+$	Pd^0L_2Cl,Li	Pd^0L_2Cl,Li	1320	
9	$PdCl_2L_2 + 2e + 1Zn^{2+}$	$Pd^0L_2Cl,ZnCl$	$Pd^0L_2Cl,ZnCl$	1480	

[a] "$Pd^0L_nL'_{n'}$" + PhI $\xrightarrow{k_{app}}$ "$PhPdXL_2$" + $(n-2)L + n'L'$ with L′= dba, PPh_3, AcO^-, Br^-, or Cl^-.

Fitton and Rick have proposed a nonclassical S_NAr mechanism for the oxidative addition of $Pd(PPh_3)_4$ to aryl halides, in which the cleavage of the C—X bond in a Meisenheimer-type intermediate would be the rate-determining step.[26]

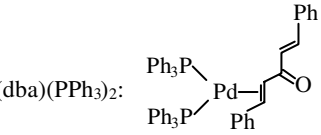
The oxidative addition might also proceed through dissociative electron transfer and in cage recombination of the triplet $\{Ar^{\bullet}, Pd^{+}, X^{-}\}$.[23],[47] Yet, this is ruled out because the rate of the oxidative addition to PhI does not depend on the solvent polarity (**Table 1**, entry 3).[48] Moreover, changing the solvent from THF to toluene does not affect the enthalpy and entropy activations, establishing that the transition state has no significant developed ionic character[40] so that it probably obeys a concerted mechanism with only minimum and localized charge development required to account for the Hammett correlation.

Before reviewing the different ways of generating a palladium(0) ligated by only two phosphine ligands, Pd^0L_2, it is worthwhile mentioning that for a stable 14-electron Pd^0L_2 complex ligated by a bulky ligand such as $P(o\text{-Tol})_3$, the oxidative addition does not proceed from the 14-electron complex $Pd^0[P(o\text{-Tol})_3]_2$ but from the 12-electron complex $Pd^0[P(o\text{-Tol})_3]$ as reported by Hartwig and Paul.[49]

B.i.b. ***$Pd^0(dba)_2$ + nL (n $\geq$ 2) as Precursors of Pd^0L_2 (L = Monodentate Phosphine Ligand).*** Association of $Pd^0(dba)_2$, an air-stable complex, with monodentate phosphines affords efficient palladium(0) catalysts.[3]–[8],[43] It was implicitly admitted that dba was a labile ligand, so that mixtures of $\{Pd^0(dba)_2 + 2L\}$ were considered suitable experimental equivalents to a quantitative use of Pd^0L_2. In this context $\{Pd^0(dba)_2 + 4L\}$ was supposed to generate Pd^0L_4. However, $Pd^0(PPh_3)_4$ is often more efficient than $\{Pd^0(dba)_2 + 2PPh_3\}$ as evidenced in the literature.[44],[45] Thus, dba must not be considered as an "innocent" Pd^0 carrier but necessarily plays a role in catalytic reactions.

Addition of 2 equiv of PPh_3 to $Pd^0(dba)_2$ in THF or DMF generates a palladium(0) complex $Pd^0(dba)(PPh_3)_2$ (Eq. 1 of **Scheme 3**) in which the dba ligand behaves as an η^2-ligand leading to two nonequivalent phosphorus atoms characterized by ^{31}P NMR spectroscopy.[48],[50]

$Pd^0(dba)(PPh_3)_2$:



$Pd^0(dba)(PPh_3)_2$ is involved in an equilibrium with $Pd^0(PPh_3)_2$ and dba (Eq. 2 of **Scheme 3**). Indeed, whereas $Pd^0(PPh_3)_2$ cannot be observed by ^{31}P NMR spectroscopy due to its too low thermodynamic concentration, it can be evidenced kinetically by cyclic voltammetry, which allows the determination of the dynamic concentration of species involved in an equilibrium, by continuous shift of this equilibrium through their electrochemical consumption (CE mechanism).[48] Addition of increasing amounts of PPh_3 results in the formation of increasing amounts of $Pd^0(PPh_3)_3$ from $Pd^0(dba)(PPh_3)_2$ (Eq. 4 of **Scheme 3**), whereas dba is progressively released in solution, evidencing that $Pd^0(PPh_3)_3$ and $Pd^0(dba)(PPh_3)_2$ are involved in an equilibrium with PPh_3 and dba (Eq. 4 of **Scheme 3**). Nearly 100 equiv of PPh_3 are required to completely displace dba from $Pd^0(dba)(PPh_3)_2$ to form $Pd^0(PPh_3)_3$ (Eq. 4 of **Scheme 3**).[51] Whatever the solvent, the value of K_0 (0.16 in DMF and 0.23 in THF at 20 °C)[48] is less than unity. This shows that for comparable dba and PPh_3 concentrations (i.e., as in usual procedures),

$$Pd^0(dba)_2 + 2L \longrightarrow Pd^0(dba)L_2 + dba \quad (1)$$

$$Pd^0(dba)L_2 \rightleftharpoons Pd^0L_2 + dba \quad K_1 \quad (2)$$

$$Pd^0L_3 \rightleftharpoons Pd^0L_2 + L \quad K_2 \quad (3)$$

Overall equilibrium

$$Pd^0(dba)L_2 + L \rightleftharpoons Pd^0L_3 + dba \quad K_0 = K_1/K_2 \quad (4)$$

Scheme 3

the overall equilibrium (Eq. 4 of **Scheme 3**) lies in favor of $Pd^0(dba)(PPh_3)_2$. This evidences that dba is not as labile as usually postulated but has a higher affinity for $Pd^0(PPh_3)_2$ than PPh_3, presumably because of its smaller size and its ability to accept electrons by retrodonation.

The oxidative addition of $\{Pd(dba)_2 + nPPh_3\}$ mixtures to PhI affords *trans*-$PhPdI(PPh_3)_2$ complexes.[48] The oxidative addition is first order in PhI and in Pd^0. It is slower when the concentration of the phosphine and/or dba increases, establishing that the reactive species is the 14-electron complex $Pd^0(PPh_3)_2$ involved in a fully dynamic equilibrium with the main nonreactive species $Pd^0(PPh_3)_3$ and $Pd^0(dba)(PPh_3)_2$ (**Scheme 4**).[48]

$$Pd^0(dba)L_2 \underset{-\,dba}{\overset{+\,dba}{\rightleftharpoons}} Pd^0L_2 \underset{-\,L}{\overset{+\,L}{\rightleftharpoons}} Pd^0L_3 \qquad K_0 = K_1/K_2$$

K_1 $\qquad$ $1/K_2$

k $\downarrow$ $+\,PhI$

$PhPdIL_2$
trans

Scheme 4

The following order of reactivity has quantitatively been established in THF and DMF (**Table 1**, entries 1–3)[48]: $Pd^0(PPh_3)_4 > \{Pd^0(dba)_2 + 2PPh_3\} > \{Pd^0(dba)_2 + 4PPh_3\}$. This definitively demonstrates that $\{Pd^0(dba)_2 + 4PPh_3\}$ is by no way equivalent to $Pd^0(PPh_3)_4$, or $\{Pd^0(dba)_2 + 2PPh_3\}$ to $Pd^0(PPh_3)_2$, as usually admitted. This occurs because the $Pd^0(PPh_3)_2$ concentration is higher when starting from $Pd^0(PPh_3)_4$ than from $\{Pd^0(dba)_2 + 2PPh_3\}$, since this latter system involves the formation of an additional thermodynamic well, $Pd^0(dba)(PPh_3)_2$.

$\{Pd^0(dba)_2 + nP(p\text{-}Z\text{-}C_6H_4)_3\}$ mixtures behave as for PPh_3 (**Scheme 3**).[51] The values of the equilibrium constants K_0^Z (Eq. 4 of **Scheme 3**) have been determined as a function of the Z substituent. For a given value of n ($n > 2$), the equilibrium between $Pd^0(dba)L_2$ and Pd^0L_3 lies more in favor of $Pd^0(dba)L_2$ when the phosphine is more basic (Hammett correlation for K_0^Z with $\rho = +4$). Similarly, when $n = 2$, Pd^0L_2 is less easily released from $Pd^0(dba)L_2$ (Eq. 2 of **Scheme 3**) when the phosphine is more basic. The oxidative addition involves Pd^0L_2 as the reactive species (**Schemae 4**), which is more reactive when the phosphine is more basic. Thus, two opposite effects are at hand when the basicity of the phosphine is varied, so that the resulting overall rate constants do not follow linear Hammett correlations. Instead, bell-shaped curves are obtained whose maximum value and position depend on n, that is, on the phosphine concentration (**Figure 1**).[51]

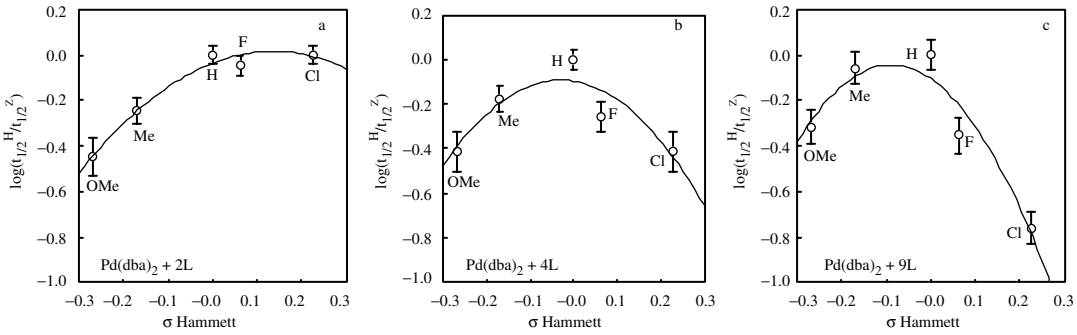


Figure 1. Hammett plot for the oxidative addition of PhI (5 mM) to the palladium(0) generated *in situ* from $Pd(dba)_2$ (1mM) and n equiv of P(p-Z-C_6H_4)$_3$ in DMF at 20 °C. (a) $n = 2$, (b) $n = 4$, and (c) $n = 9$.

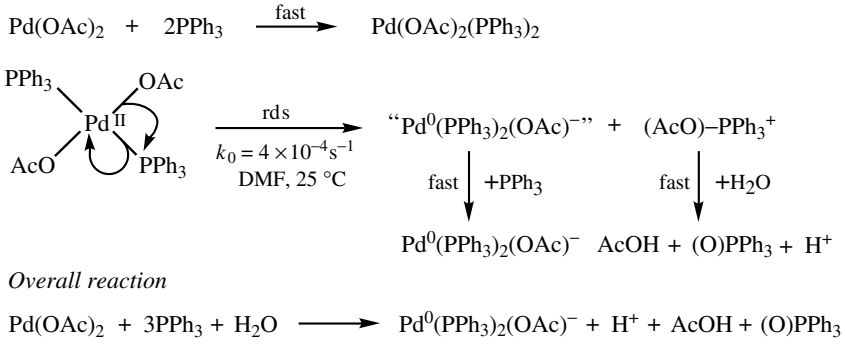
These results seem to be in apparent contradiction with the belief that, for comparable cone angles, the oxidative addition is sensitive to electronic factors, being faster when the phosphine is more basic. This contradiction is only apparent and results from the fact that the overall reactivity in the oxidative addition is governed by two factors: the intrinsic reactivity of Pd^0L_2 in the oxidative addition expressed by k^Z (**Scheme 4**) and the concentration of Pd^0L_2, which is controlled by the values of the equilibrium constants ${K_1}^Z$ and ${K_0}^Z$, as well as by the concentration of dba and L. When the phosphine is more basic, the complex Pd^0L_2 is more nucleophilic and k^Z increases. However, the Pd^0L_2 concentration is smaller because the equilibrium constants ${K_1}^Z$ and ${K_0}^Z$ decrease. As a result of these two antagonist effects, bell-shaped curves are obtained. Consequently, a palladium(0) reagent involving a basic phosphine may be overall less reactive than another one involving a less basic phosphine, depending on the side of the curve where the system lies (**Figure 1**). This is even more crucial since the position of the maximum depends on the concentration of the catalyst precursor as well as on the equivalents of phosphine (**Figure 1**). Furthermore, this shall also depend on the reaction medium that affects k^Z, ${K_1}^Z$, and ${K_0}^Z$.

These antagonist effects provide an explanation for the reactivity of palladium(0) complexes generated from mixtures of $Pd^0(dba)_2$ and PPh_3 when compared to TFP.[52] In DMF, $\{Pd^0(dba)_2 + n\text{TFP}\}$ is more reactive than $\{Pd(dba)_2 + nPPh_3\}$ whatever n ($n \geq 2$). In THF, the order of reactivity depends on the value of n. $\{Pd(dba)_2 + n\text{TFP}\}$ is less reactive than $\{Pd^0(dba)_2 + nPPh_3\}$ when $n = 2$ or 4, whereas the reverse order of reactivity is observed when $n > 6$.[52] The determination of the equilibrium constant K_0 (Eq. 4 in **Scheme 3**) shows that in THF and DMF, ${K_0}^{PPh_3} < {K_0}^{TFP}$. When $n = 2$, only the equilibrium 2 in **Scheme 3** is involved. Since ${K_1}^{PPh_3} < {K_1}^{TFP}$, the available concentration of $Pd^0(PPh_3)_2$ is less than that of $Pd^0(TFP)_2$. Since PPh_3 gives rise to a more reactive system than TFP ($k^{PPh_3}{K_1}^{PPh_3} > k^{TFP}{K_1}^{TFP}$), it ensues that $k^{PPh_3} > k^{TFP}$. For higher values of n ($n > 2$), the equilibrium 4 in **Scheme 3** has to be taken into consideration, for which one has again ${K_0}^{PPh_3} < {K_0}^{TFP}$. Thus, even if $Pd^0(TFP)_2$ remains intrinsically less reactive than $Pd^0(PPh_3)_2$, its concentration becomes considerably higher than that of $Pd^0(PPh_3)_2$ when n is large, resulting then in a higher overall reactivity for the palladium(0) associated to the TFP ligand.

In conclusion, dba in not the labile and "innocent" ligand usually considered in the literature. Whatever the monodentate phosphine investigated here, $\{Pd^0(dba)_2 + nL\}$

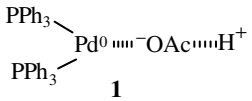
mixtures result in the formation of stable complexes $Pd^0(dba)L_2$, which are thermodynamic wells and henceforth are major nonreactive complexes. These complexes release dba through an equilibrium that determines the concentration of the 14-electron complexes Pd^0L_2, which are the actual reactive species in oxidative additions.[53]

B.i.c. ***Pd(OAc)$_2$ + nL (n $\geq$ 3) as Precursor of Three-Coordinate Anionic Pd^{0}L$_2$(OAc)$^-$ (L = PPh$_3$).*** $\{Pd(OAc)_2 + nL\}$ mixtures were initially introduced as catalysts in Heck reactions[54] but are also involved in Suzuki cross-coupling of organoboranes.[4] In both cases, a palladium(0) is mechanistically required to activate aryl halides C—X bonds. However, the origin of the palladium(0) center has remained unknown, since no clearly identified reducer is present in the catalytic reactions. A quantitative kinetic study of this system has established that addition of 3 equiv of PPh_3 to $Pd(OAc)_2$ quantitatively generates a stable palladium(0) complex[55],[56] through an intramolecular reduction of the palladium(II) to palladium(0),[55],[57] a process by which the phosphine is oxidized to phosphine oxide, $(O)PPh_3$ (**Scheme 5**).



Scheme 5

The palladium(0) generated in this reaction is an anionic species ligated by the anion AcO^-, $Pd^0(PPh_3)_2(OAc)^-$, which then undergoes oxidative additions.[58] It is important to note that this palladium(0) complex is generated together with protons resulting from the hydrolysis of the phosphonium salt (**Scheme 5**). Its reactivity is then affected by the protons and consequently by bases. Indeed, the interaction of the ligated acetate with a proton (compound **1**) affords a more naked and thus more reactive complex whose reactivity is presumably close to that of the ideal $Pd^0(PPh_3)_2$ complex. Addition of a base neutralizes the protons and therefore stabilizes $Pd^0(PPh_3)_2(OAc)^-$, which is then less reactive in oxidative additions (**Table 1**, entries 4–5).[58],[59]



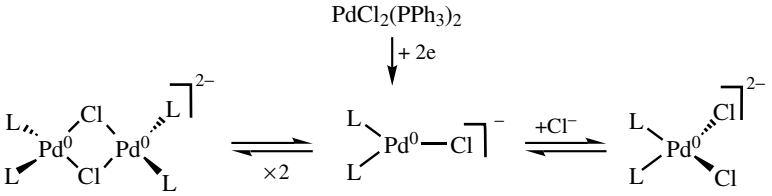
1

The oxidative addition of the palladium(0) complexes generated from $Pd(OAc)_2$ and $P(p\text{-}Z\text{-}C_6H_4)_3$ follows a linear Hammett correlation with a negative slope ($\rho = -2.8$) establishing, as expected, that the more basic the phosphine, the more reactive the palladium(0) complex.[57]

B.i.d. ***PdX_2L_2 as Precursor of Three-Coordinate Anionic $Pd^0L_2X^-$ ($X = Halide, L = PPh_3$).*** Reduction of palladium(II) complexes ligated by two phosphines should formally yield Pd^0L_2 complexes quantitatively. Indeed, $PdCl_2(PPh_3)_2$[9] and $PhPdI(PPh_3)_2$[10] are efficient catalysts for cross-coupling of aryl halides and Grignard reagents, which are also able to act as chemical reductants for the palladium(II) complexes. Whenever the nucleophiles are not reducing agents, independent reducers are used (e.g., metallic hydrides) and added in stoichiometric amount relative to the palladium(II) catalysts.[11] Negishi and co-workers have established that the chemical reduction of $PdX_2(PPh_3)_2$ by organolithium reagents does not provide the expected $Pd^0(PPh_3)_2$, but species that were characterized as $Li_nX_nPd^0(PPh_3)_2$ (X = Cl, Br, n = 1 or 2?) or their oligomers.[60] Indeed, the ^{31}P NMR signal of the resulting complexes strongly depends on the halide X and on the countercation associated to the chemical reducer. The oxidative addition of such anionic palladium(0) complexes to PhI was too fast to be monitored by classical techniques such as ^{31}P NMR spectroscopy.[60]

The electrochemical reduction of $PdX_2(PPh_3)_2$ (X = Cl, Br, I) complexes in THF was shown to proceed through an overall bielectronic process, generating palladium(0) complexes characterized by their oxidation peak detected on the reverse scan of the voltammograms.[61],[62] When $PdX_2(PPh_3)_2$ reduction is performed in the presence of PhI (1 equiv), the oxidation peak of the electrogenerated palladium(0) is no longer detected, showing that its oxidative addition to PhI occurs and is complete in less than a few seconds. The palladium(0) oxidation peak is progressively restored upon increasing the scan rate, that is, upon decreasing the time scale. The rate constant of the oxidative addition could then be easily determined from variations of the oxidation peak current (which is proportional to the palladium(0) concentration) versus scan rate (**Table 1**, entries 6–7),[62] although the extremely short reaction times exclude any kinetic determination by the usual spectroscopic techniques: for example, $t_{1/2} = 80$ ms when the palladium(0) is generated by reduction of $PdCl_2(PPh_3)_2$ (2 mM) in the presence of PhI (2 mM) in THF at 20 °C.

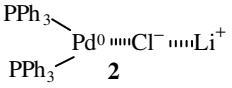
The ^{31}P NMR spectrum of the palladium(0) solution, generated through an exhaustive electrolysis of $PdCl_2(PPh_3)_2$ (2 F/mol) exhibits three signals whose relative magnitude depends on the concentration of chloride anions, added as n-Bu_4NCl prior to electrolysis.[62] All of them disappear upon oxidative addition to PhI. This establishes that three different palladium(0) complexes are generated by reduction of $PdCl_2(PPh_3)_2$. The rate of the oxidative addition is slowed down upon decreasing the palladium concentration and increasing the chloride ion concentration. A detailed kinetic study has established that chloride ions coordinate the palladium(0) center to form three anionic palladium(0) complexes (including one dimer) with n-Bu_4N^+ as the countercation. These three species are involved in two equilibria (**Scheme 6**), which are fast versus the voltammetric time scale but slow versus the ^{31}P NMR time scale, so that one observes an apparent single Pd^0 species in voltammetry but three distinct Pd^0 species by ^{31}P NMR spectroscopy.[62]



Scheme 6

The dimer is intrinsically the most reactive species, but under usual conditions its concentration is very low so that the monoanionic species $Pd^0(PPh_3)_2Cl^-$ is the main reactive one (**Table 1**, entry 7).[62] Reduction of $PdBr_2(PPh_3)_2$ affords two mononuclear complexes $Pd^0(PPh_3)_2Br^-$ and $Pd^0(PPh_3)_2Br_2^{2-}$, the monoanionic species being again the most reactive one (**Table 1**, entry 6). In the absence of purposely added halide ions and under usual concentration of 2 mM, $Pd^0(PPh_3)_2Cl^-$ is more reactive than $Pd^0(PPh_3)_2Br^-$ (**Table 1**, entries 6–7).[62]

The formation of $Li_nX_nPd^0(PPh_3)_2$ complexes, generated by chemical reduction of $PdCl_2(PPh_3)_2$ by an organolithium, was simulated by reducing $PdX_2(PPh_3)_2$ at the electrode, in the presence of free cations such as Li^+ introduced as $LiBF_4$.[62] Their reactivity in the oxidative addition to PhI was investigated by performing fast cyclic voltammetry as described above. The oxidative addition is faster in the presence of cations (**Table 1**, entries 7–9).[62] Indeed, interaction by ion pairing of cations with the chloride anion ligated to the palladium(0) affords a more naked and thus more reactive palladium(0) complex (compound **2**) whose properties resemble those of the ideal $Pd^0(PPh_3)_2$.[59]



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Transient short-lived and thus very reactive species analogous to those generated by chemical reduction can be generated by electrochemical reduction. Moreover, kinetic data on their reactivity are then available. Electrochemical investigations have thus definitively established that the sought $Pd^0(PPh_3)_2$ species cannot exist in solution as soon as it is generated in the presence of halide ions. Instead, anionic palladium(0) species are formed by coordination of the palladium(0) center by halide ions, as Negishi and co-workers proposed in their seminal work.[60] The rate of the oxidative addition then depends on anions but also on cations. This stresses that, in a catalytic cycle, presumed "innocent" ions such as anions (halide ions released by the palladium(II) precursor or by the aryl halides during the catalytic reaction) or cations (delivered by the reducers or nucleophiles) may interfere in the catalytic cycle. Similar behavior has been observed when the palladium(0) is generated from $Pd(OAc)_2$ and phosphine (see **Sect. B.i.c**). For example, the anionic species $Pd^0L_2(OAc)^-$ is more reactive in the presence of protons, which play the same complexing role *vis-à-vis* $Pd^0L_2(OAc)^-$ as that of cations *vis-à-vis*-$Pd^0L_2Cl^-$.

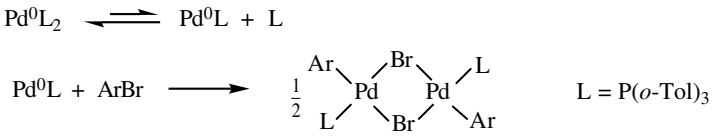
B.i.e. ***Conclusion.*** Although in almost every case, the reactive species in oxidative addition is a palladium(0) complex ligated by two monodentate phosphines L, the overall reactivity is very dependent on the precursor of the active palladium(0) complex, as established in **Table 1**. Indeed, the reactive palladium(0) complex, Pd^0L_2, is often present at trace concentrations because it is involved in endergonic equilibria with major but nonreactive Pd^0 complexes, ligated by phosphine in Pd^0L_3 or by dba in $Pd^0(dba)L_2$. When the palladium(0) is generated from palladium(II) precursors ligated to halide or acetate ions, the active species are present at quantitative concentration compared to the precursor but these are three-coordinate anionic species PdL_2X^- (X = Cl, Br, OAc) and not the sought after Pd^0L_2 complex. Their reactivity is strongly affected by the anions but also by cations or protons delivered in the Pd^{II}/Pd^0 reduction process. Thus, in all cases, the palladium(0) catalytic center keeps some "chemical memory" of its precursor. Furthermore, this also affects the structure of the arylpalladium(II) complexes formed in

the oxidative addition to aryl halides (or triflates) and consequently their reactivity with nucleophiles, so that the whole catalytic cycle is affected.

B.ii. Structure of Arylpalladium(II) Complexes Formed in Oxidative Addition to Aryl Halides/Triflates as a Function of the Precursors of the Palladium(0) and the Ligand

B.ii.a. trans-*ArPdXL$_2$ Complexes (X = Halide, L = PAr$_3$).* Oxidative addition of aryl halides to $Pd^0(PPh_3)_4$[26] or to the palladium(0) generated from $Pd^0(dba)_2$ and monodentate phosphines (PPh_3,[48] P(*p*-Z-Ph)$_3$,[51] TFP[52]) give *trans*-$ArPdXL_2$ complexes. This reaction first affords the *cis* complexes but their lifetimes are so short that they are generally not observed. A stable *cis*-$(F_3Cl_2C_6)PdI(PPh_3)_2$ complex has been isolated by Casado and Espinet.[27] Its *cis–trans* isomerization is shown to proceed by a four bimolecular pathway mechanism.

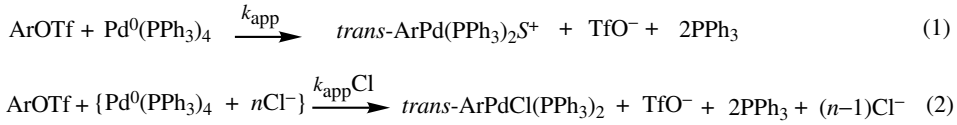
B.ii.b. *Dimeric [ArPdXL]$_2$ Complexes (X = Halide, L = P(o-Tol)$_3$).* In the case of bulky phosphines such as P(*o*-Tol)$_3$, Paul et al.[63] have established that the oxidative addition performed from $Pd^0[P(o\text{-Tol})_3]_2$ via the 12-electron complex $Pd^0[P(o\text{-Toly})_3]$ does not afford the classical *trans*-$ArPdXL_2$ complexes, but a dimer $[ArPdXL]_2$ formed by fast dimerization of the intermediate T-shaped complex ArPdXL (**Scheme 7**).



Scheme 7

B.ii.c. *Cationic* trans-*ArPdL$_2$S$^+$ Complexes (S = Solvent, L = PPh$_3$).* Oxidative addition of aryl triflates to a free-chloride complex such as $Pd^0(PPh_3)_4$ gives cationic *trans*-$ArPd(PPh_3)_2S^+$ (S = THF, DMF) characterized by conductivity measurements (Eq. 1 of **Scheme 8**).[41] Neutral *trans*-$ArPdCl(PPh_3)_2$ complexes are formed as soon as chloride ions are added to $Pd^0(PPh_3)_4$ (Eq. 2 of **Scheme 8**). The faster oxidative addition observed in the presence of chloride ions ($k_{app}^{Cl} > k_{app}$)[41] confirms the involvement of three-coordinate anionic $Pd^0(PPh_3)_2Cl^-$ complexes.[62]

Cationic $ArPdL_2S^+$ complexes are probably formed by oxidative addition of $Pd^0(PPh_3)_4$ complexes to aryl diazonium salts.



Scheme 8

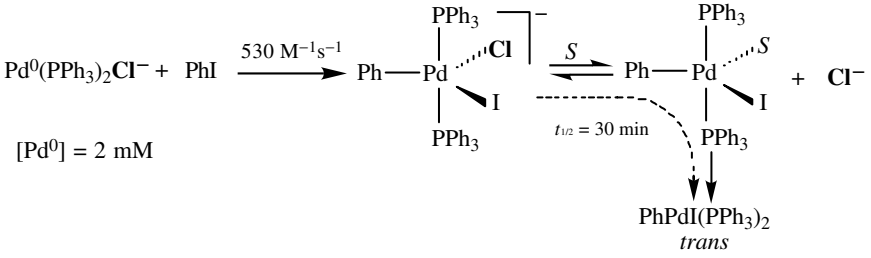
B.ii.d. *Equilibrium Between Neutral ArPdXL$_2$ and Cationic ArPdL$_2$S$^+$ Complexes (X = Halide, L = PPh$_3$).* Although *trans*-$PhPdX(PPh_3)_2$ (X = I, Br) exhibited a single ^{31}P NMR signal in DMF, they pertain to an endergonic equilibrium that involves the

cationic *trans*-$PhPd(PPh_3)_2(DMF)^+$ complex as evidenced by chronoamperometry, which permits the determination of both dynamic and thermodynamic concentrations of electroactive species.[64]

$$PhPdX(PPh_3)_2 \rightleftharpoons PhPd(PPh_3)_2S^+ + X^- \qquad K_X\,(X = Cl, Br, I)$$

$$K_{Cl} = 0.5 \times 10^{-4}\,M \qquad K_{Br} = 2.8 \times 10^{-4}\,M \qquad K_I = 5.6 \times 10^{-4}\,M \text{ (DMF, 20 °C)}$$

B.ii.e. ***Five-Coordinate Anionic Complexes: $ArPdXX'L_2^-$ (X and X′ = Halide, L = PPh_3).*** Under usual conditions, the palladium(0) species formed by reduction of $PdCl_2(PPh_3)_2$ is the anionic complex $Pd^0(PPh_3)_2Cl^-$.[62] Its oxidative addition to PhI affords eventually the expected *trans*-$PhPdI(PPh_3)_2$. However, at shorter times, an anionic five-coordinate intermediate complex $PhPdI(Cl)(PPh_3)_2^-$ is formed in which the chloride ion, borne by the reactive palladium(0), remains ligated to the palladium(II) center (**Scheme 9**).[65] This 18-electron complex $PhPdI(Cl)(PPh_3)_2^-$ is involved in a fast uphill equilibrium in which the chloride ion is expelled to form a neutral five-coordinate complex $PhPdI(S)(PPh_3)_2$ (**Scheme 9**, S = THF). This latter subsequently generates the stable *trans*-$PhPdI(PPh_3)_2$ complex.



Scheme 9

Chloride ions have thus an inhibiting effect on the *trans*-$PhPdI(PPh_3)_2$ formation as evidenced by the reciprocal dependence of the overall rate constant versus chloride concentration.[65] These results stress the important role of the anion borne by the palladium(0) involved in the oxidative addition, since the anion nature and concentration control the rate of formation of the *trans*-$PhPdI(PPh_3)_2$ complex as well as the existence and concentration of the five-coordinate anionic $PhPdI(Cl)(PPh_3)_2^-$ and neutral $PhPdI(S)(PPh_3)_2$ complexes, which are also potentially reactive with nucleophiles (see **Sect. B.iii.e**).

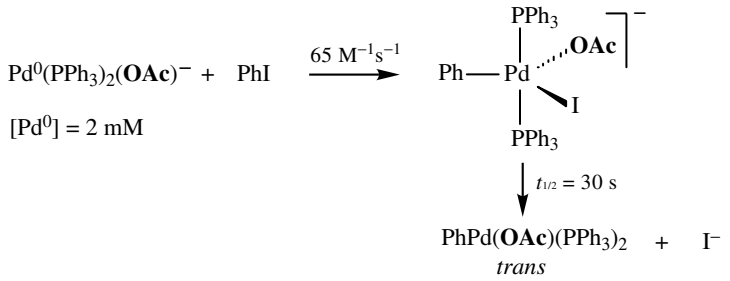
B.ii.f. ***Neutral trans-$ArPd(OAc)L_2$ Complexes (L = PPh_3).*** Addition of acetate ions to *trans*-$PhPdX(PPh_3)_2$ (X = Cl, Br, I) provides *trans*-$PhPd(OAc)(PPh_3)_2$ via a reversible nucleophilic substitution of the halide (Eq. 1 of **Scheme 10**).[55],[58],[66] The equilibrium constants K have been determined in THF and DMF from ^{31}P NMR studies.[58] As for *trans*-$PhPdX(PPh_3)_2$ (see **Sect. B.ii.d**), *trans*-$PhPd(OAc)(PPh_3)_2$ is involved in an equilibrium with the cationic $PhPd(PPh_3)_2S^+$ complex (Eq. 2 of **Scheme 10**).[58],[64]

$$PhPdX(PPh_3)_2 + AcO^- \rightleftharpoons PhPd(OAc)(PPh_3)_2 + X^- \qquad K \qquad (1)$$

$$PhPd(OAc)(PPh_3)_2 \rightleftharpoons PhPd(PPh_3)_2S^+ + AcO^- \quad K_{OAc} = 1.4 \times 10^{-3}\ mol\ dm^{-3} \qquad (2)$$

Scheme 10

The *trans*-ArPd(OAc)L_2 complexes are formed in the oxidative addition of aryl iodides to $Pd^0(PPh_3)_2(OAc)^-$, generated *in situ* from $\{Pd(OAc)_2 + 3PPh_3\}$ mixture.[58] The oxidative addition proceeds again via a short-lived five-coordinate anionic arylpalladium(II) complex in which the acetate ion borne by the palladium(0) remains ligated to the palladium(II) center (**Scheme 11**).[58]



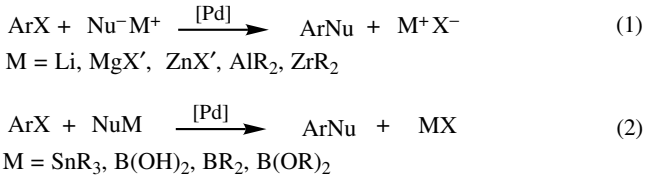
Scheme 11

The *trans*-ArPd(OAc)L_2 complexes are also formed when the oxidative addition is performed from $Pd^0(PPh_3)_4$ in the presence of acetate anions.[58]

B.ii.g. *Conclusion.* Oxidative addition of aryl halides to palladium(0) complexes provides a large variety of arylpalladium(II) complexes: neutral, anionic, or cationic complexes, as a function of the aryl electrophile (e.g., ArX versus ArOTf) and the exact structure of the palladium(0) involved in the oxidative addition. Moreover, these complexes may be linked by a dynamic equilibrium. The structure of the arylpalladium(II) complexes affects their reactivity with nucleophiles in the so-called transmetallation step.

B.iii. Reaction of Nucleophiles with Arylpalladium(II) Complexes (Transmetallation)

Two kinds of nucleophiles undergo catalytic cross-coupling with aryl halides: "hard" nucleophiles, which are associated to a metallic countercation (organometallic derivatives, Eq. 1 of **Scheme 12**), and "soft" nucleophiles, which are associated to a metalloid center (organostannane and borane derivatives, Eq. 2 of **Scheme 12**).



Scheme 12

All nucleophiles are supposed to react with arylpalladium(II) complexes in a transmetallation reaction during the catalytic reaction (**Scheme 1**). For a given Pd^0 precursor and a given ligand, cross-coupling of PhI with "soft" nucleophiles (organostannanes) generally requires higher temperature than with "hard" nucleophiles.[1],[2],[7],[31] It is why the

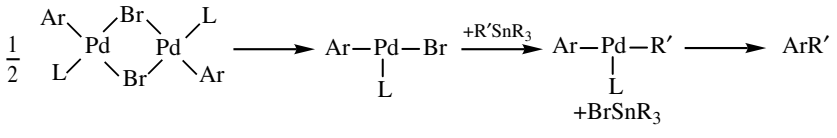
transmetallation step is often considered as the rate-determining step of the catalytic cycle, which follows a fast oxidative addition in which a *trans*-$ArPdIL_2$ complex is formed.[31],[39] Determination of a reaction order in PhI of zero in Stille reactions definitively establishes that the transmetallation is rate determining in cross-coupling reactions involving low reactive "soft" nucleophiles.[39] Once the transmetallation is performed, whenever a diorgano *trans*-$ArPdNuL_2$ complex is formed (**Scheme 1**), the reductive elimination should proceed via a preliminary *trans–cis* isomerization of this complex (**Scheme 1**) which might be rate determining.[35]–[37] Mechanisms have recently been established or postulated in which the formation of a *trans*-$ArPdNuL_2$ is bypassed. Indeed, the reductive elimination can either proceed from 14-electron T-shaped complexes ArPdNuL[34],[39],[67] (see **Sect. B.iii.d**) or result from the evolution of an 18-electron five-coordinate anionic species $ArPdX(Nu)L_2^-$[65] (see **Sect. B.iii.e**).

The reactivity of nucleophiles in the transmetallation step as well as the mechanism of the transmetallation and consequently the reductive elimination step depend both on the structure of the nucleophile and the arylpalladium(II) complex formed in the oxidative addition.

B.iii.a. ***Cationic $ArPdL_2S^+$ Complexes (L = PPh_3).*** To our knowledge, isolated 14-electron cationic $ArPdL_2S^+$ complexes have never been tested as reagents in transmetallation processes although they are involved in equilibrium with neutral *trans*-$ArPdXL_2$ (X = Cl, Br, I, OAc) complexes in DMF[64] (see **Sects. B.ii.d** and **B.ii.f**). $ArPdL_2S^+$ complexes are probably more reactive with nucleophiles than the related neutral *trans*-complexes because they are three-coordinate and more electrophilic. In this context, the facile and very fast backward reaction of their formation equilibrium proves unambiguously that these cationic intermediates react even with poor nucleophiles such as Cl^-, Br^-, I^-, and AcO^-. Whenever cationic *trans*-$ArPdL_2S^+$ complexes react with nucleophiles, they should lead to the formation of *trans*-$ArPdNuL_2$ complexes.

Cationic *trans*-$ArPd(PPh_3)_2S^+$ complexes are quantitatively produced in oxidative addition of aryl triflates to free-chloride palladium(0) complexes (**Scheme 8**).[41] However, Stille reactions from aryl triflates are more efficient when performed in the presence of added chloride ions.[22],[39],[68] Neutral *trans*-$ArPdClL_2$ complexes are then formed (**Scheme 8**)[41] by reaction of chloride ions with the cationic complex $ArPdL_2S^+$, whose concentration decreases. The accelerating effect of chloride ions evidences that the cationic complex is not involved in the transmetallation process but instead the neutral *trans*-$ArPdClL_2$ is, probably via a T-shaped complex ArPdClL, as evidenced by Farina and Krishnan in related reactions[39] (see **Sect. B.iii.d**).

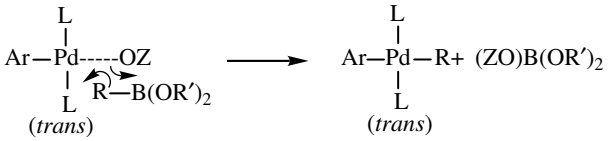
B.iii.b. ***Dimeric $[ArPdXL]_2$ Complexes (X = Halide, L = P(o-Tol)$_3$).*** Dimeric $[ArPdXL]_2$ (L = P(*o*-Tol)$_3$) complexes react with nucleophiles via the T-shaped complex (Louie and Hartwig) to form a T-shaped ArPdNuL complex prone to undergo a fast reductive elimination (**Scheme 13**).[67]



L = P(*o*-Tol)$_3$, Ar = *p*-Tol, R′ = Ph, SAr, NMe_2, R = Me, Bu

Scheme 13

B.iii.c. trans-*ArPd(OAc)L$_2$ Complexes (L = PPh$_3$).* *trans*-ArPd(OAc)$(PPh_3)_2$ complexes are reagents for the transmetallation step in Suzuki cross-coupling when acetate ions are added as a base. Indeed, Ishiyama and co-workers have reported that *trans*-ArPd(OAc)$(PPh_3)_2$ complexes, formed by substitution of bromide by acetate in *trans*-ArPdBr$(PPh_3)_2$ (see **Sect. B.ii.f**), undergo transmetallation reactions with diboronic esters to produce arylboronic esters.[66] Moreover, the overall reaction is faster than that performed on *trans*-ArPdBr$(PPh_3)_2$. This result provides one explanation among others for the requirement of a base in Suzuki reactions.[4] Transmetallation on *trans*-ArPd(OAc)$(PPh_3)_2$, ArPd(OH)$(PPh_3)_2$, or ArPd(OMe)$(PPh_3)_2$ complexes is indeed expected to be easier than that performed on *trans*-ArPdX$(PPh_3)_2$ (X = halide) due, on one hand, to the lower affinity of oxygen ligand for Pd^{II} compared to that of halide ions (compare **Sects. B.ii.d** and **B.ii.f**) and, on the other hand, to the high oxophilicity of the boron center (**Scheme 14**).[4],[66]



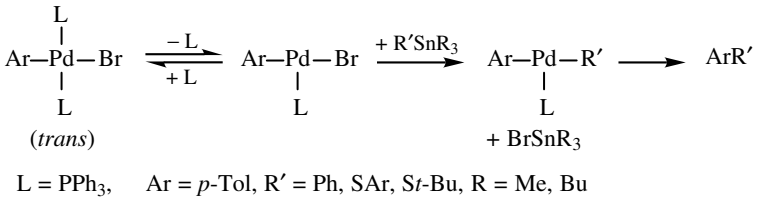
L = PPh_3, Z = H, Ac, Me

Scheme 14

Aliprantis and Canary have reported the detection (by electrospray mass spectroscopy) of the diorgano complexes (3-pyridyl)Pd(Ar)$(PPh_3)_2$ as post-transmetallation species in a Suzuki coupling of 3-bromopyridine and aryl boronates.[69] Neither (3-pyridyl)Pd(OH) $(PPh_3)_2$ nor (3-pyridyl)Pd(OMe)$(PPh_3)_2$ is observed, suggesting that the transmetallation step is faster than the reductive elimination from the diorgano (3-pyridyl)Pd(Ar)$(PPh_3)_2$ complexes.

B.iii.d. trans-*ArPdXL$_2$ Complexes (X = Halide, L = Monophosphine).* As postulated in **Scheme 1**, reaction of nucleophiles on *trans*-ArPdXL_2 complexes should give diorganopalladium complexes, *trans*-ArPdNuL_2. An endergonic *trans–cis* isomerization is then formally required to allow reductive elimination from *cis*-ArPdNuL_2 with formation of the cross-coupling product ArNu. *trans*-ArPdXL_2 complexes are 16-electron square planar complexes. Their electronic structure induced by their geometry does not permit an easy direct attack of a nucleophile to form an 18-electron complex by an associative mechanism,[70] although addition of a fifth ligand such as phosphines or alkynes to square planar 16-electron complexes has been proposed to promote *trans–cis* isomerization of *trans*-(Vinyl)PdRL_2[36] or reductive elimination from stable *cis*–RPdR′L_2 complexes.[35] Conversely, any transmetallation on a *trans*-ArPdXL_2 complex will be favored by a preliminary dissociation step, for example, deligation of a ligand, to form unsaturated 14-electron T-shaped ArPdXL complex, prone to react with nucleophiles.

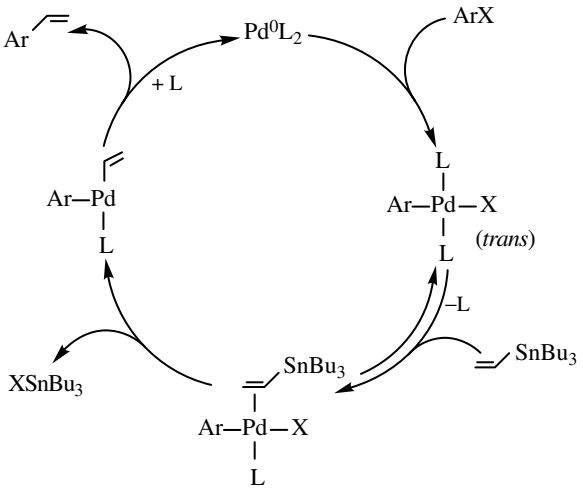
Reaction of Soft Nucleophiles with trans-ArPdXL$_2$ Complexes. Louie and Hartwig have reported that stoichiometric reactions of "soft" nucleophiles such as organostannane derivatives on isolated 16-electron *trans*-ArPdX$(PPh_3)_2$ generally proceed via one ligand dissociation (inverse first-order dependence on added PPh_3) to form 14-electron T-shaped ArPdX(PPh_3) complexes. Their reaction with nucleophiles affords unsaturated diorgano T-shaped complexes ArPdNu(PPh_3), which undergo a fast reductive elimination (**Scheme 15**).[67]



Scheme 15

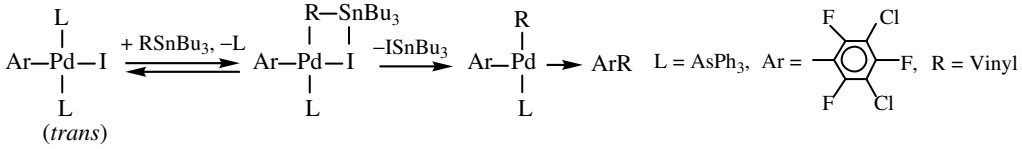
Although Farina and Krishnan have not reported stoichiometric reactions of vinylstannanes on isolated *trans*-ArPdXL$_2$ complexes, they have postulated the formation of intermediate π-complexes with vinylstannanes after a ligand dissociation (dissociative process), which is then a key step for the transmetallation (**Scheme 16**).[39]

The easier displacement of TFP (or AsPh$_3$) by the vinylstannane double bond compared to that of PPh$_3$ is probably at the origin of the large rate acceleration observed in Stille reactions when TFP (or AsPh$_3$) is associated to the Pd^0 catalyst instead of PPh$_3$.[39] The reductive elimination proceeds then from a T-shaped ArPdNuL complex (**Scheme 16**).



Scheme 16

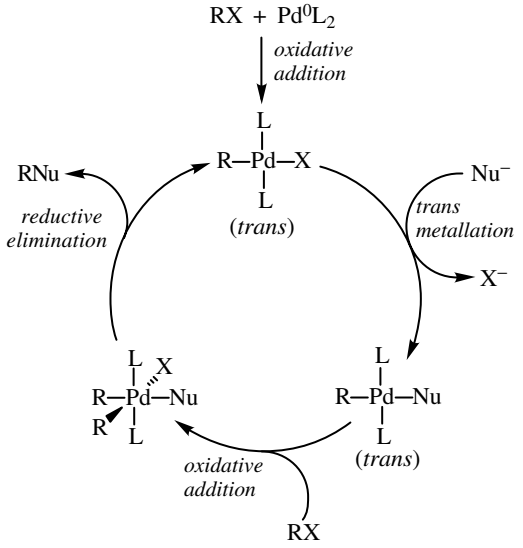
Casado and Espinet have proposed an associative mechanism on the basis of kinetic studies on the reaction of organostannane derivatives with isolated *trans*-ArPdX(AsPh$_3$)$_2$ complexes. The decomplexation of one ligand by the nucleophile generates a bridged intermediate complex. This latter provides a T-shaped complex, which readily gives the coupling product (**Scheme 17**).[34]



Scheme 17

In all cases reported above, the intermediate diorganopalladium(II) complexes have not been isolated or characterized but are postulated on the basis of kinetic investigations.

A mechanism involving Pd^{IV} complexes has been proposed by Milstein and Stille in the particular case of very reactive electrophiles.[12] The stoichiometric reaction of *trans*-$(PhCH_2)PdBr(PPh_3)_2$ with Me_4Sn gives PhEt in low yield. This reaction is considerably accelerated when performed in the presence of added $PhCH_2Br$. This has been rationalized by the involvement of an oxidative addition of the intermediate *trans*-$(PhCH_2)PdMe(PPh_3)_2$ complex (initially formed in the transmetallation step) to $PhCH_2Br$. This reaction generates a six-coordinate Pd^{IV} complex, from which the reductive elimination occurs more easily (**Scheme 18**).[12],[35] An alternative mechanism for the cross-coupling is thus proposed, based on Pd^{II}/Pd^{IV} complexes (**Scheme 18**). The oxidative addition of Pd^{II} complexes to very reactive electrophiles to form Pd^{IV} complexes is supported by the isolation and characterization of Pd^{IV} complexes.[71]

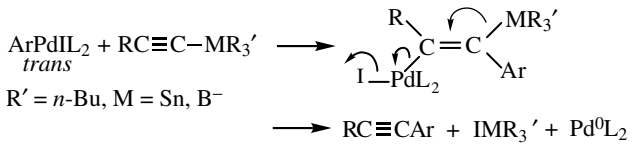


Scheme 18

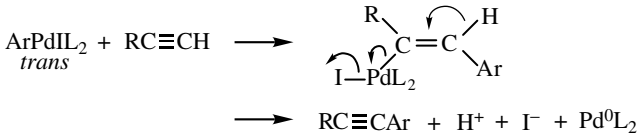
Although probably restricted to electrophiles RX, which are extremely reactive in oxidative addition (R = alkyl or benzyl), this mechanism shows how the coupling product may be formed via a *trans*-$RPdNuL_2$ complex by bypassing the endergonic formation of the *cis*-$RPdNuL_2$.

An alternative mechanism for the transmetallation has been proposed in the particular case of "soft" alkynyl nucleophiles. Indeed, upon investigation of the comparative reactivity of nucleophiles in cross-coupling with aryl iodides catalyzed by $PdCl_2(PPh_3)_2$, Negishi has observed an unexpected high reactivity of "soft" nucleophiles such as $RC{\equiv}C{-}SnR'_3$ or $RC{\equiv}C{-}BR'_3{}^-$ compared to that of the related zinc derivative.[1] In this particular case, Negishi proposes a mechanism involving, after the oxidative addition, a *carbopalladation* step as in a Heck-type reaction on simple alkynes, followed by a *β-elimination* of the metalloid moiety (**Scheme 19**).[1]

Negishi proposes a similar mechanism for the Pd-catalyzed Sonogashira coupling of aryl halides and alkynes when performed without Cu^I catalysts (**Scheme 20**).[72]

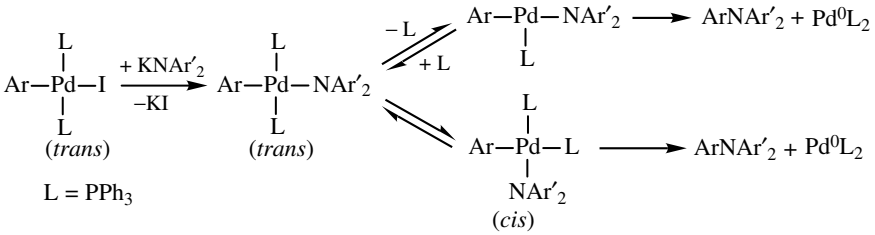


Scheme 19



Scheme 20

Reaction of Hard Nucleophiles with trans-ArPdXL$_2$ Complexes. Stable diorgano *trans*-ArPd(NAr$_2$′)(PPh$_3$)$_2$ complexes have been isolated by Driver and Hartwig, by reacting *trans*-ArPdI(PPh$_3$)$_2$ and "hard" nucleophiles such as amides, KNAr$_2$′ (**Scheme 21**).[33] The formation mechanism of the cross-coupling product ArNAr$_2$′ from *trans*-ArPd(NAr$_2$′)(PPh$_3$)$_2$ was investigated. At low phosphine concentration, the formation of ArNAr$_2$′ is inhibited by the phosphine and consequently the reductive elimination proceeds from a T-shaped complex ArPd(NAr$_2$′)L formed by phosphine dissociation (**Scheme 21**, upper route).[33]



Scheme 21

Conversely, at high phosphine concentration, the formation of ArNAr′$_2$ is not affected by the phosphine concentration, presumably because the concentration of the T-shaped complex becomes too small to play any significant kinetic role. The reductive elimination proceeds then through the *cis*-ArPd(NAr$_2$′)L$_2$ complex formed by isomerization of the *trans*-ArPd(NAr$_2$′)L$_2$ (**Scheme 21**, lower route).[33]

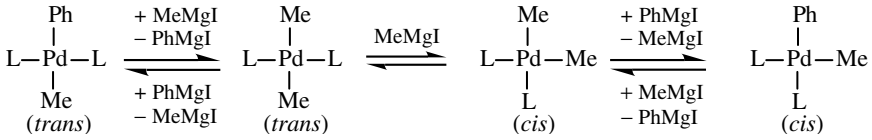
"Hard" nucleophiles (RLi, RMgX′, RZnX′) react with isolated *trans*-ArPdX(PPh$_3$)$_2$ complexes to give the cross-coupling product and a palladium(0) complex (Fauvarque and Jutand,[9],[29],[30] Negishi et al.[31]). A detailed mechanistic study by Negishi et al.[31] has established that the rate of formation of the cross-coupling product was similar to the rate of disappearance of the *trans*-ArPdX(PPh$_3$)$_2$ complex, so that no intermediate, such as the *trans*-ArPdNu(PPh$_3$)$_2$ postulated in **Scheme 1**, accumulates after the transmetallation step. This implies that neither the *trans–cis* isomerization of *trans*-ArPdNu(PPh$_3$)$_2$, nor the reductive elimination from the *cis*-ArPdNu(PPh$_3$)$_2$ complex is rate determining. An induction period observed for the formation of the cross-coupling product in a reaction between PhI and (*E*)-1-octenylzinc chloride in the presence of Pd^0(PPh$_3$)$_4$ (50%), evidenced the

initial buildup of *trans*-PhPdI(PPh_3)$_2$ without formation of the cross-coupling product. This establishes that the transmetallation on *trans*-PhPdI(PPh_3)$_2$ is the rate-determining step, which follows a fast oxidative addition in the very first catalytic cycles.[31]

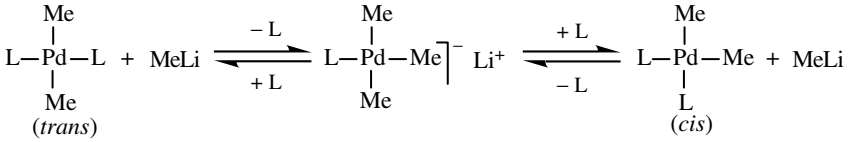
Loar and Stille have detected and characterized by ^{31}P NMR spectroscopy *cis*- and *trans*-(*Z*)-(styryl)PdMeL$_2$ (styryl = —CH═CH—Ph, L = PPh_2Me) by reacting MeLi (1 equiv) with *trans*-(*Z*)-(styryl)PdBrL$_2$ at low temperatures.[36] A T-shaped intermediate is probably involved in the transmetallation since the reaction is found to be slower in the presence of added phosphine. *trans*-(*Z*)-(Styryl)PdMeL$_2$ then isomerizes to *cis*-(*Z*)-(styryl)PdMeL$_2$ with an overall rate accelerated by the presence of an extra ligand. This is an example where the addition of a fifth ligand to a 16-electron complex is invoked. The cross-coupling compound Ph—CH═CH—Me is eventually formed after a reductive elimination from the *cis* diorgano complex.[36] This reactions sequence is an elegant demonstration of what is going on when taking as an hypothesis the nucleophilic attack on a *trans* complex formed in the oxidative addition (**Scheme 1**).

The mechanism of a cross-coupling reaction of PhI and MeMgI catalyzed by *trans*-PhPdI(PEt_2Ph)$_2$ has been investigated by Ozawa et al.,[73] focusing on the isomerization of the isolated *trans*-PhPdMe(PEt_2Ph)$_2$ complex (formed in the transmetallation process) to the *cis*-PhPdMe(PEt_2Ph)$_2$ complex, only able to undergo a reductive elimination with formation of toluene. The *trans–cis* isomerization is promoted by the nucleophile (**Scheme 22**).[73]

These substitution/isomerization steps probably involve intermediate palladate complexes such as those established for the *trans–cis* isomerization of $PdMe_2L_2$ complexes (**Scheme 23**).[37],[73]



Scheme 22



Scheme 23

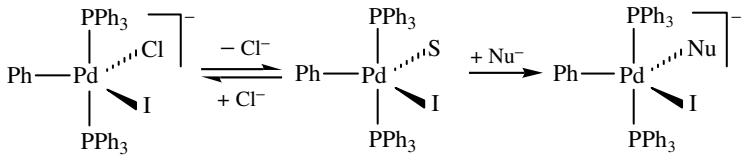
The promotion of reductive elimination from stable *trans*-ArPdAr′(PEt_3)$_2$ complexes by nucleophiles (ArLi) has also been reported by Negishi and co-workers, leading, however, to some homocoupling compound ArAr.[32]

All the mechanisms reported above postulate that *trans*-ArPdXL$_2$ complexes are reactive complexes for the transmetallation step. However, the effective reactivity of hard nucleophiles, observed on isolated *trans*-ArPdXL$_2$ complexes, does not establish that they are real intermediates in the catalytic reaction. Indeed, nucleophilic attack of Grignard[9] or zinc enolates[29],[30] on *trans*-PhPdI(PPh_3)$_2$ complex do provide the cross-coupling product but at a rate that is noticeably smaller than the rate of the overall catalytic reaction. This suggests that *trans*-ArPdX(PPh_3)$_2$ complexes are not involved in the fast propagating

catalytic cycle and that mechanistic and kinetic investigations on stoichiometric transmetallation steps performed from isolated *trans*-ArPdX$(PPh_3)_2$ complexes may be not relevant to the real catalytic reaction involving hard nucleophiles. For example, in a catalytic reaction, the real intermediate could well be a *cis*-ArPdX$(PPh_3)_2$ complex, which must first be formed in the oxidative addition.[27] A fast nucleophilic attack on the *cis* complex would then directly give a *cis*-ArPdNu$(PPh_3)_2$ complex and the cross-coupling product after reductive elimination from this *cis* diorgano complex. However, the involvement of *cis*-ArPdX$(PPh_3)_2$ complexes as intermediates prone to react with nucleophiles has never been established owing to their too short lifetime in their *cis–trans* isomerization (see **Sect. B.ii.a**).

A mechanism is now proposed, which involves five-coordinate anionic $ArPdXX'L_2^-$ complexes.

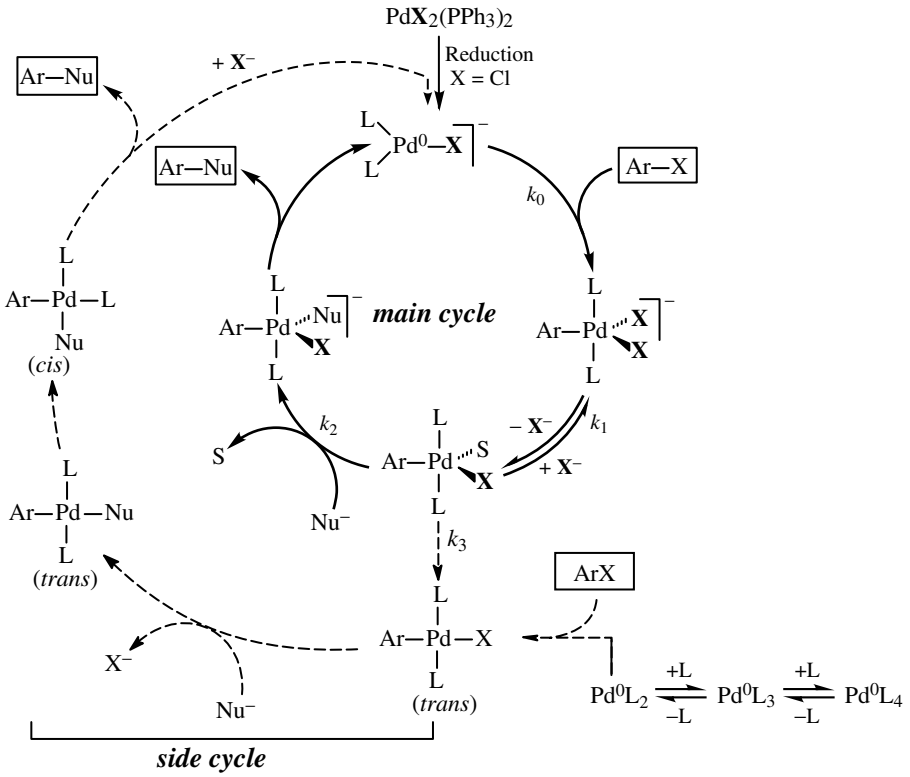
B.iii.e. ***Five-Coordinate Anionic Complexes: ArPdXX′L₂⁻ (X and X′ = Halide, L = PPh₃).*** The palladium(0) complex, generated by reduction of $PdCl_2(PPh_3)_2$, is an anionic complex $Pd^0(PPh_3)_2Cl^-$ and its oxidative addition to PhI generates a five-coordinate anionic arylpalladium(II) complex, $PhPdI(Cl)(PPh_3)_2^-$, which provides over long time periods (≈hours), the *trans*-PhPdI$(PPh_3)_2$ complex (see **Sect. B.ii.e**).[65] This slow reaction proceeds through a very fast but extremely uphill equilibrium in which the anionic pentacoordinated phenylpalladium(II) complex releases one chloride ion and a neutral solvated five-coordinate PhPdI(*S*)$(PPh_3)_2$ complex (**Scheme 9**). Consequently, the chloride ion brought by the reactive palladium(0) controls the formation of three different phenylpalladium(II) complexes prone to react with nucleophiles (**Scheme 9**). However, as seen above (**Sect. B.iii.d**) *trans*-PhPdI$(PPh_3)_2$ cannot be an intermediate under catalytic conditions because its reaction with "hard" nucleophiles is slower than the overall catalytic reaction. Moreover, it is formed from $Pd^0(PPh_3)_2Cl^-$ at a too slow rate (≈hours) to participate in any fast catalytic cycle usually completed within tens of minutes. The nucleophile must then attack the five-coordinate neutral complex, PhPdI(*S*)$(PPh_3)_2$ as the poor nucleophilic chloride ion does (**Scheme 24**).



Scheme 24

This reaction would generate a five-coordinate anionic complex: $PhPdI(Nu)L_2^-$, in which the Ph and Nu ligands are now adjacent and so in a favorable position for a fast reductive elimination (**Scheme 25**, main cycle), which gives the cross-coupling product and a three-coordinate anionic Pd^0 complex, able to initiate the second catalytic cycle (**Scheme 25**, main cycle).[65]

Such a sequence would readily bypass the *trans*-PhPd(Nu)L_2 formation. As a proof of the validity of this mechanism involving five-coordinate anionic arylpalladium(II) species, the 2-thiophenyl anion is found to react 2.5 times slower with the *trans*-PhPdI$(PPh_3)_2$ complex (**Scheme 1**) than with the anionic phenylpalladium(II) complex generated by the oxidative addition to $Pd^0(PPh_3)_2Cl^-$ (**Scheme 25**).



Scheme 25

B.iv. Conclusion and Final Comments

It appears that transmetallation of most "soft" nucleophiles (Stille reaction) proceeds from *trans*-$ArPdXL_2$ complexes via 14-electron transient T-shaped ArPdXL complexes, whereas transmetallation of "hard" nucleophiles proceeds through 18-electron anionic $ArPdXX'L_2^-$ complexes. The mechanism described in **Scheme 25** explains most of the mechanistic features observed in cross-coupling catalyzed by most usual palladium systems. However, there are several subtleties that must be discussed owing to the delicate tuning of the reaction kinetics by anions and cations. Indeed, halide anions and cations are progressively released due to the progressive reaction of ArX and Nu^-m^+ (m: countercation of nucleophiles) as the catalytic reaction proceeds. These modifications may induce a progressive change of the main mechanism in **Scheme 25** involving anionic species. The released ions may be free (noted $A^- + C^+$) or ion-paired (noted A^-C^+) so that four formal situations must be considered (**Scheme 26**).

$$ArX + (Nu^-m^+) \longrightarrow ArNu + (m^+X^-) \quad (1)$$

$$ArX + Nu^- + m^+ \longrightarrow ArNu + (m^+X^-) \quad (2)$$

$$ArX + (Nu^-m^+) \longrightarrow ArNu + m^+ + X^- \quad (3)$$

$$ArX + Nu^- + m^+ \longrightarrow ArNu + m^+ + X^- \quad (4)$$

Scheme 26

The metal cation m^+ delivered by the nucleophile may play a crucial role by controlling the concentration of free anions and thus by inducing a possible competition between the "anionic" main cycle in **Scheme 25** and the classical mechanism in **Scheme 1**. When the released halide ions are ion-paired (m^+X^-) (Eqs. 1 and 2 of **Scheme 26**) or involved in covalent derivatives ($XSnR_3$, XBR_2, $XB(OR)_2$), their free concentration does not increase during ArX conversion and no anionic Pd^0 or Pd^{II} complexes are formed. The mechanism of **Scheme 25** (main cycle) cannot develop except if free halide ions are purposely added (e.g., R_4N^+, X^-) in stoichiometric amount relative to the catalyst. When halide anions are ion-paired, the cross-coupling reaction presumably proceeds through **Scheme 1** with *trans*-$ArPdXL_2$ as intermediate. Conversely, when halide anions are free (Eqs. 3 and 4 of **Scheme 26**) or when free halide anions are voluntarily added, $Pd^0L_2X^-$ and $ArPdX_2L_2^-$ are formed and the main "anionic" cycle of **Scheme 25** should be dominant. However, the situation might be more complicated since **Schemes 25** and **1** are connected at the level of the intermediate five-coordinate neutral complex $ArPdX(S)L_2$. This latter can either react with the nucleophile or evolve to the less reactive *trans*-$ArPdXL_2$ complex. The probability of remaining within the main "anionic" cycle of **Scheme 25** is $k_2[Nu]/(k_3 + k_2[Nu])$. This probability decreases as the catalytic reaction proceeds since the nucleophile concentration decreases. Moreover, the comparatively stable *trans*-$ArPdX(PPh_3)_2$ accumulates at each cycle, so that a progressive shift from the main "anionic" cycle of **Scheme 25** to that of **Scheme 1** may occur through the *trans*-$ArPdX(PPh_3)_2$ complex. However, when halide ions are released as free ions, the cycle of **Scheme 1** is reconnected to the main "anionic" cycle of **Scheme 25** via the extremely fast formation of the anionic $Pd^0L_2X^-$ species (left side of **Scheme 25**).[62] A new cycle progressively develops (left side cycle, then half right part of the main cycle) at the expense of the main cycle of **Scheme 25**. The same situation must happen for Pd^0L_4-catalyzed reactions when halide ions are free. Indeed, formation of anionic species, $Pd^0(PPh_3)_2X^-$ occurs while the catalytic reaction proceeds (**Scheme 25**).[62]

On the other hand, when the free halide ion concentration increases, the "anionic" main cycle of **Scheme 25** gets slower because the oxidative addition gets slower[62] (see **Sect. B.i.d**) and because the concentration of the reactive $ArPdX(S)(PPh_3)_2$ decreases due to a shift of the equilibrium toward $ArPdX_2(PPh_3)_2^-$. However, this does not affect the branching between the main and side mechanisms.

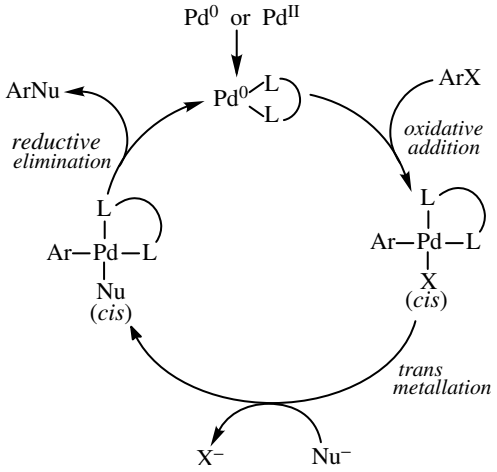
The ion-paired or free-ion nature of the nucleophile is also crucial on the selection of mechanisms. When the nucleophile is ion-paired (Eq. 3 of **Scheme 26**), it is intrinsically less reactive with $ArPdX(S)L_2$ than the free nucleophile. $k_2[Nu]$ is then smaller and the deviation through the *trans*-$ArPdXL_2$ complex (left side cycle of **Scheme 25**) is favored with respect to the same situation but in the presence of non-ion-pairing cations. Thus, the metal nature also controls the deviation toward the side mechanism through its influence on the nucleophile reactivity. Conversely, when the nucleophile is a free anion, the metal cation has no influence (Eq. 4 of **Scheme 26**) except if it makes ion pairs with the halides (Eq. 2 of **Scheme 26**) and thus controls the availability of free halide ions as described above.

Therefore, occurrence of mechanisms of **Schemes 1** or **25** and of the two limit cycles in **Scheme 25** is finely tuned by ion-pairing equilibria involving halide anions (delivered by the Pd^{II} precursor and by the aryl halides) and metal cations (delivered by the nucleophiles or by the reductant of the Pd^{II} precursor), which are released during the catalytic reaction. The mechanism may also be sensitive to changes in the reaction medium, for example, a solvent that will affect ion pairing. The mechanism reported in **Scheme 25** provides an

explanation for the strong dependency on metals of the nucleophilic organometallic reagents in catalytic cross-coupling, as first reported by Negishi et al.[31]

C. MECHANISM OF THE CROSS-COUPLING CATALYZED BY PALLADIUM(0) COMPLEXES LIGATED BY BIDENTATE DIPHOSPHINE LIGANDS (L-L)

With bidentate ligands (L-L) giving a *cis* coordination, the mechanism of the cross-coupling simplifies because only *cis*-ArPdX(L-L) and consequently *cis*-ArPdNu(L-L) complexes are formed, making the reductive elimination feasible (**Scheme 27**).



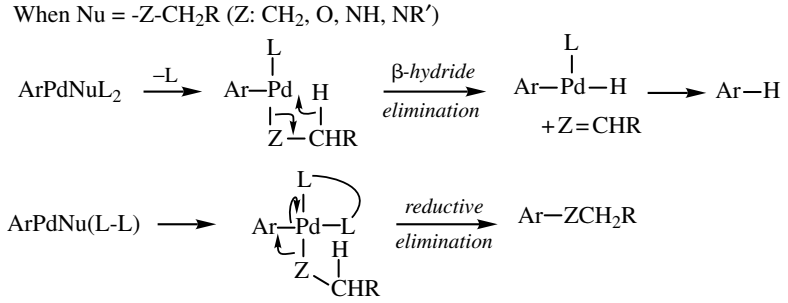
Scheme 27

Bidentate ligands have been introduced by Hayashi et al. [42] to prevent a β-hydride elimination that may occur in $ArPdNuL_2$ complexes when the nucleophile possesses a labile hydride and when L is a monodentate ligand, leading to the undesired by-product ArH[9] (**Scheme 28**).

The β-hydride elimination requires a vacant coordination site on the Pd^{II} center, easily available with monodentate phosphine ligands (**Scheme 28**). With bidentate diphosphine ligands, the high local concentration of the ligand around the palladium(II), due to the intramolecular character of the ligation, makes the second ligation stronger and consequently the β-hydride elimination less probable than the reductive elimination (**Scheme 28**).

Brown and Cooley have reported a fine mechanistic investigation of a cross-coupling between a vinyl halide (*para*-methoxybromostyrene) and $PhCH_2MgCl$, catalyzed by $PdCl_2$(dppf).[74],[75] Starting from an isolated Pd^0(dppf)($CH_2{=}{=}CH_2$) complex and performing the reaction at adapted low temperatures allowed the isolation or identification of the complex formed in the oxidative addition, *cis*-(σ-styryl)PdBr(dppf), as well as the complex formed after the transmetallation, *cis*-(σ-styryl)Pd(CH_2Ph)(dppf), that is, every intermediate complex postulated in **Scheme 27** (in which ArX shall be replaced by VinylX), evidencing the reductive elimination from a *cis* diorganopalladium(II) complex.

Most other mechanistic investigations have been conducted on separated elemental steps, from isolated Pd^0/Pd^{II} complexes ligated by bidentate ligands.



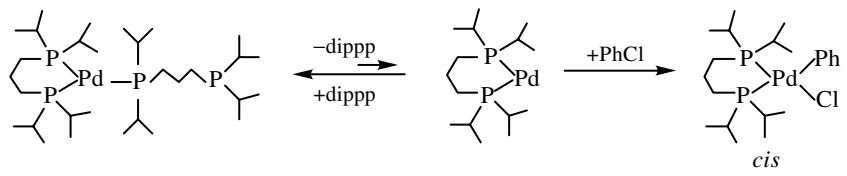
Scheme 28

C.i. Rate and Mechanism of the Oxidative Addition of Aryl Halides to Palladium(0) Complexes Ligated by Bidentate Diphosphine Ligands

The postulated reactive complex in the oxidative addition step is a 14-electron complex, Pd^0(L-L), whatever the palladium(0) or palladium(II) precursors (**Scheme 27**). $PdCl_2$(L-L) complexes in which L-L is a P,P ligand catalyze cross-coupling reactions, dppf being one of the best ligands for the cross-coupling of C-nucleophiles.[42] However, the nature and reactivity of the palladium(0) complexes formed by the chemical reduction of $PdCl_2$(L-L) are unknown, due to their instability when generated in the absence of any extra ligand such as olefins.[74]–[76] The formation of an anionic Pd^0(dppf)Cl^- [76] and subsequent five-coordinate anionic ArPdXCl(dppf)$^-$ after oxidative addition to ArX, has not been reported. Up to now, the electrochemical approach, well adapted to investigate the reactivity of short-life species (see **Sect. B.i.d**.), has found some limitation since the electrochemical reduction of $PdCl_2$(L-L) (L-L = dppe, dppf, DIOP) results in the formation of stable palladium(I) complexes due to a competitive fast reaction between the electrogenerated Pd^0 complex and the initial $PdCl_2$(L-L) complex.[77] So the role of chloride ions in the oxidative addition step could not be clarified.

The 18-electron complexes Pd^0(L-L)$_2$ do not react with aryl halides[25],[78] so that the potential sources of the 14-electron Pd^0(L-L) complexes, are either Pd^0(L-L)L′$_2$ or Pd^0(L-L)L″ complexes, where L′ (monophosphine[9]) and L″ (monoligated diphosphine[79] or olefin[76],[78],[80]) are ligands, which are more labile than L-L when the oxidative addition to ArX proceeds, giving *cis*-ArPdX(L-L) complexes selectively.[9],[76],[78]–[80]

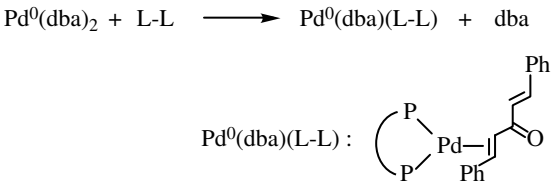
C.i.a. ***Pd^0(η^1-L-L)(L-L) as Precursor of Pd^0(L-L) (L-L = dippp).*** Portnoy and Milstein have investigated the mechanism and kinetics of the oxidative addition of Pd^0(η^1-dippp)(η^2-dippp) to aryl chlorides, which are usually low reactive derivatives. The reaction proceeds mainly via the 14-electron complex, Pd^0(η^2-dippp) (**Scheme 29**).[79] A minor route gives *trans*-PhPdCl(η^1-dippp)$_2$ from the 14-electron complex Pd^0(η^1-dippp)$_2$.



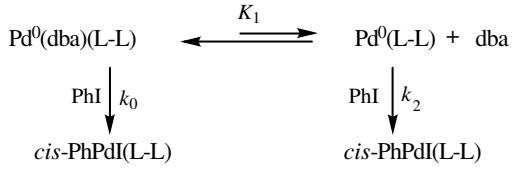
Scheme 29

C.i.b. *$Pd^0(dba)_2$ + L-L as Precursor of Pd^0(L-L) (L-L = Diphosphine Ligands).* Mixtures of $Pd^0(dba)_2$ and 1 equiv of L-L (L-L = dppm, dppe, dppp, dppb, DIOP, dppf and BINAP) in THF and DMF lead to Pd^0(dba)(L-L) complexes[78] (**Scheme 30**) whose structures have been elucidated by ^{31}P NMR spectroscopy[50],[78] and by X-ray spectroscopy for dppe.[50]

Whatever the ligand, dppf, DIOP, or BINAP, Pd^0(dba)(L-L) is the main complex in solution.[78] The oxidative addition to PhI, which gives *cis*-PhPdI(L-L) complexes, is slower in the presence of excess dba, showing that the most reactive complex is Pd^0(L-L), which is involved in an endergonic equilibrium with Pd^0(dba)(L-L) (**Scheme 31**). However, Pd^0(dba)(L-L) also reacts in parallel with PhI ($k_2 >> k_0$) (**Scheme 31**).[78]



Scheme 30



Scheme 31

The reactivity of these different catalytic systems in the oxidative addition to PhI has been compared on the basis of kinetic investigations. The following order of reactivity has been observed (**Table 2**):[78]

$$\{Pd^0(dba)_2 + 2\ PPh_3\} >> \{Pd^0(dba)_2 + 1\ DIOP\} > \{Pd^0(dba)_2 + 1\ dppf\} > \{Pd^0(dba)_2 + 1\ BINAP\}$$

The bidentate ligands investigated in **Table 2** are more basic than PPh_3 and their P–Pd–P bite angle is smaller than the P–Pd–P angle when PPh_3 is considered. This suggests that Pd^0(P,P) would be intrinsically more reactive than $Pd^0(PPh_3)_2$. However, the

TABLE 2. Comparative Reactivity of Palladium(0) Complexes in Oxidative Addition to Phenyl Iodide as a Function of the Ligand in THF

Number	Precursor of Pd^0 (2 mM)	T (°C)	PhI (mM)	$t_{1/2}$ (s)
1	$Pd^0(dba)_2$ + 1 BINAP	40	0.2	16300
2	$Pd^0(dba)_2$ + 1 dppf	40	0.2	110
3	$Pd^0(dba)_2$ + 1 DIOP	40	0.2	34
4	$Pd^0(dba)_2$ + 2 PPh_3	20	0.01	3.5

systems associated to one bidentate ligand are considerably less reactive than that associated to two PPh_3. This means that, for identical initial $Pd^0(dba)_2$ concentration, the concentration of $Pd^0(PPh_3)_2$ is considerably higher than that of Pd^0(P, P) and that thermodynamic factors are more important than electronic and steric factors. This emphasizes the role of dba, which controls the concentration of the more reactive 14-electron complexes PdL_2 or Pd(L-L) in their equilibrium with the major 16-electron complexes ligated by dba.[53]

The 16-electron complex Pd^0(dppf)(η^2-CH_2═CH-CO_2Me) reacts with aryl halides and triflates without the involvement of the 14-electron complex Pd^0(dppf), except when cations (Eu^{3+}) are added, which are able to coordinate the methylacrylate ligand.[80]

C.ii. Transmetallation of Nucleophiles on *cis*-ArPdX(L-L) Complexes

cis-ArPdX(L-L) complexes tested in transmetallation with nucleophiles have been synthesized (i) by ligand exchange on dimeric [ArPdXP(*o*-Tol_3)]$_2$ complexes (L-L = BINAP, Tol-BINAP, dppf),[81] (ii) by ligand exchange on *trans*-ArPdX(PPh_3)$_2$ complexes (L-L = dppf),[33] and (iii) by oxidative addition to nonisolated Pd^0(L-L)(η^2-cyclooctatetraene) complex formed *in situ* by reduction of $PdCl_2$(L-L) by dilithium cyclooctatetraenide (L-L = dppp, dppf).[76]

Under stoichiometric conditions, the postulated diorganopalladium(II) *cis*-ArPdNu(L-L) complexes are formed with "hard" nucleophiles: Grignard reagents,[76] alkoxides,[81],[82] and amides.[33] *cis*-ArPdNu(L-L) complexes in which the nucleophile is a carbanion (L-L = dppp, dppf)[76] have been characterized *in situ* by ^{31}P NMR spectroscopy performed at low temperatures but have not been isolated due to fast reductive elimination. The stability of *cis*-ArPdNu(L-L) (L-L = BINAP, Tol-BINAP, dppf) with alkoxides as nucleophiles strongly depends on the ligand and the aryl group for a given alkoxide.[81],[82] Complexes in which the nucleophile is an amide (with L-L = dppf) [33] are more stable and have been isolated.

C.iii. Reductive Elimination from *cis*-ArPdNu(L-L) Complexes

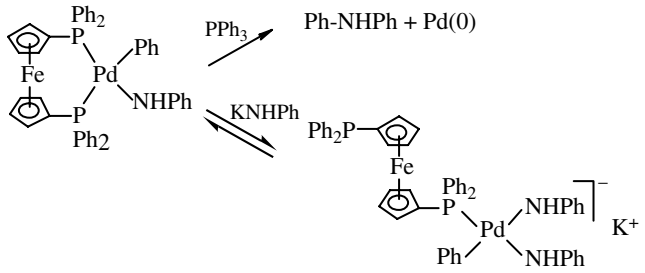
Brown and Guiry have investigated the bite angle influence on the rate of the reductive elimination from *cis*-ArPdMe(L-L) complexes (L-L = dppp, dppf), leading to C—C bond formation (Ar—Me). The larger the bite angle at palladium, the faster the reductive elimination, dppf being more efficient than dppp. The results are consistent with a concerted mechanism operating from the four-coordinate *cis* complex according to **Scheme 27**.[76]

Driver and Hartwig have shown that reductive elimination proceeds from isolated *cis*-ArPd(NHR)(dppf)) (or *cis*-ArPd(NR_2)(dppf)) complexes to afford Ar-NHR (or Ar-NR_2) via a concerted mechanism occurring from the four-coordinate *cis* complex (**Scheme 32**, upper route).[18],[33] The formation of the C—N bond is favored upon increasing the electrophilicity of the aryl group. The more nucleophilic the amido group, the faster the reductive elimination.

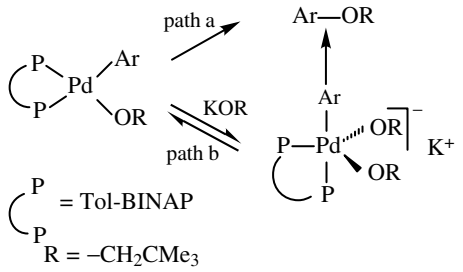
However, when excess nucleophile (KNHPh) is added to a solution of the *cis*-PhPd(NHPh)(dppf), a new anionic four-coordinate complex is formed with dppf acting as a monodentate ligand, PhPd(NHPh)$_2$(η^1-dppf)$^-$ (**Scheme 32**, lower route).[33] It is interesting to note that this situation is closer to catalytic conditions.

The formation of a C—O bond by reductive elimination from *cis*-ArPd(OR)(L-L) (L-L = Tol-BINAP, BINAP, dppf) has been reported by Buchwald and co-workers.[81],[82] In the absence of any alkoxide, the reductive elimination proceeds from the *cis* complex

(**Scheme 33**, path a).[81] In the presence of excess alkoxide (KOR) a linear dependence of the rate of the reductive elimination with the alkoxide concentration suggests an associative mechanism with the formation of a five-coordinate anionic intermediate $ArPd(OR)_2(Tol\text{-}BINAP)^-$, which undergoes a faster reductive elimination than the four-coordinate *cis*-ArPd(OR)(Tol-BINAP) (**Scheme 33**, path b).[81]



Scheme 32



Scheme 33

It seems that fast C—C bond formation occurs via a concerted mechanism from the *cis*-diorganopalladium(II) complex whereas the C—O and C—N bond formations are more sluggish and require an extra reagent, which may be the nucleophile present in large excess in the catalytic reaction.

D. SUMMARY

This section evidences that the nature and reactivity of the actual reactive palladium(0) species in oxidative additions strongly depend on its precursor. Indeed, $Pd^0(PPh_3)_2$, the most commonly postulated species supposed to participate in all catalytic systems, is never present in stoichiometric amounts compared to its Pd^{II} or Pd^0 precursor. It is either generated as a minor complex when Pd^0L_4 and $Pd^0(dba)_2$ are precursors or does not exist at all when generated in the presence of anions. Instead, three-coordinate anionic $Pd^0L_2X'^-$ complexes are formed in which one halide X′ (or one acetate) remains ligated to the palladium(0). Consequently, the rate of oxidative additions to aryl halides ArX depends on the precursor system. This will affect the overall reactivity whenever the oxidative addition is the rate-determining step. This also affects the nature and consequently the reactivity of the arylpalladium(II) intermediates formed by the ensuing oxidative addition to ArX.[83]

In the presence of anions, five-coordinate anionic complexes $ArPdXX'(PPh_3)_2^-$ are formed, in which the anion X'^- borne by the palladium(0) remains ligated to the palladium(II) center. One anion is reversibly substituted by the solvent in $ArPdXX'(PPh_3)_2^-$, so that the anion controls the concentration of the five-coordinate neutral complex $ArPdX(S)(PPh_3)_2$, which is engaged in a fast reaction with "hard" nucleophiles Nu^-, to generate again an anionic five-coordinate $ArPdX(Nu)(PPh_3)_2^-$ complex. This latter complex presumably gives ArNu through a fast reductive elimination. The *trans*-$ArPdXL_2$ species is thus bypassed in the transmetallation step.

In the presence of low reactive "soft" nucleophiles, the *trans*-$ArPdXL_2$ complex is formed in the oxidative addition. The cross-coupling proceeds then through 14-electron T-shaped ArPdXL and ArPdNuL complexes.

Therefore, in both cases, the formation of the *trans*-$ArPdNuL_2$ complex and consequently the endergonic formation of the *cis*-$ArPdNuL_2$ complex are bypassed.

Only few mechanistic studies are presently available on cross-coupling involving a palladium(0) catalyst ligated by a bidentate ligand, which take into account the precursor of the palladium(0) and its chemical environment. Although the postulated mechanism appears consistent in most cases, the decelerating effect of dba observed on the rate of the oxidative additions when $Pd^0(dba)_2$ is the precursor of the reactive Pd^0 complex, the accelerating effect of alkoxide nucleophiles on the reductive elimination from *cis*-ArPd(OR)(L-L) by formation of anionic $ArPd(OR)_2(L\text{-}L)^-$ complexes, and the formation of anionic $ArPd(NHR)_2(\eta^1\text{-}L\text{-}L)^-$ complexes in the presence of excess amides, that is, under conditions that are closer to the real catalytic reactions, reveal more complicated mechanisms than the usually postulated ones, in terms of the nature of the rate-determining step or/and the reactive intermediates.

These examples illustrate the danger in inferring a mechanistic conclusion from kinetic information derived from isolated stable complexes expected to be intermediates, without taking into account their real chemical history and reactive environment.

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